Antibiotics: Miracle drugs or pig food?

John F. Prescott

The crisis of antibiotic resistance in medically important bacteria has taken the bloom off the antibiotic miracle. Infection specialists talk darkly of entering the postantibiotic era. In the public debate going on over this issue, the use of feed antibiotics in farm animals is increasingly questioned. Clearly, the major cause of resistance to antibiotics in human pathogens is medical prescription use of these drugs. There is, however, the danger that agricultural use of antibiotics is becoming a ready scapegoat for problems of resistance in human medicine, made easier because of the complexities of the topic and because agricultural use of these drugs has technicalities that take some understanding.

It was the unexpected discovery in the 1950s that antibiotics increased growth rates and improved the efficiency of food utilization in pigs and chickens that has led to their use as growth promoters ever since. About 40% of antibiotic production in the United States is used in animal feed, but exact figures are unavailable (1). This represents 55% to 60% of the total production of penicillin G and tetracyclines, with 50% of the total animal feed medication being tetracyclines (1). In the United States, this may represent up to 8500 tons, a staggering total in terms of the microgram antibacterial potency of these chemicals (Table 1). Since Canada's drug policy generally reflects (and lags) that of the United States, percentage usage in this country is likely similar, but details are not available.

Contrary to popular misconception, agricultural use of antibiotics is extensively regulated. Under the food and drug legislation in both Canada and the United States, there are 3 uses of antibiotics in agriculture: as feed antibiotics, as over-the-counter (OTC) drugs, and as veterinary prescription drugs.

Feed antibiotics are those that farmers can order through licensed feed mills for growth promotion (2–50 g/ton of feed), for subtherapeutic use (200 g or less/ton of feed), or for disease treatment (over 200 g/ton of feed). Subtherapeutic use, the most contentious and the largest of the uses, encompasses prevention of specified diseases but includes growth promotion in the face of certain diseases. Most feed antibiotics are used for this purpose, particularly in swine. Many of the feed antibiotics are drugs that are unique to agriculture (carbadox, flavomycin, monensin, salinomycin, virginiamycin). Other feed antibiotics in common use in animals (bacitracin, lincomycin, sulfonamides, tetracyclines, tylosin) are not commonly used in human medicine. Only penicillin G, which is often used in pig feed in combination with sulfonamides and tetracyclines, is commonly used in human medicine (Table 2).

Table 1. Estimated annual antibiotic use in livestock in the United States, 1985 ('000 kg) (1)

Species	Therapeutic use	Subtherapeutic use	Growth promotion
Cattle[a]	458	1100	340
Swine	250	3578	1391
Poultry[b]	304	580	315

[a]Mostly beef cattle
[b]Mostly meat chickens

Table 2. Antimicrobial agents prescribed to people in Canada, 1996 (2)

Antimicrobial agent	Number of prescriptions (millions)
Amoxicillin	6.78
Cephalosporin	3.31
Erythromycin	2.72
Trimethoprim-sulfonamide	1.76
Quinolones	1.66
Extended-spectrum macrolide	1.48
Other broad-spectrum penicillin	0.95
Antifungals	0.93
Tetracyclines	0.89

Feed antibiotics are licensed for designated purposes. In pigs, most feed antibiotics are used in newly weaned piglets, a critical time for infections in these young animals, and only to a lesser extent in older pigs being raised for slaughter, where their use is generally regarded as unnecessary and not cost effective. In cattle, their use is mainly in calves, which like all young animals are particularly susceptible to infectious diseases, but also in beef cattle on their introduction into feedlots, where mixing of animals from different sources is likewise associated with infections. By contrast, dairy cows usually encounter antibiotics only if they develop mastitis, after which their milk must be discarded until no antibiotics remain. Only certain antibiotics can be administered to adult ruminants (cattle, sheep, goats), since these animals depend for their lives on microbial fermentation of grass and are liable to be killed by some antibiotics. An unusual range of antimicrobial drugs are fed to meat chickens during their 5- to 6-week lifespan, since as young animals they are also

Department of Pathobiology, University of Guelph, Guelph, Ontario N1G 2W1.

This is a development of a talk given by J.F. Prescott at the recent Antimicrobial Resistance Conference sponsored by Health Canada, Montreal, May 1997.

susceptible to infectious diseases, such as coccidiosis. Antibiotics would rarely be administered to laying hens because of the need to discard their eggs until they are free from the drug.

Over-the-counter drugs are available to farmers for injection or administration in water to animals. These are essentially the same drugs as are used in feed, with the addition of older aminoglycosides not used in human medicine (neomycin, spectinomycin, streptomycin) and erythromycin, a drug used quite commonly for mild pneumonic disease in people but not favored by farmers since its injection is painful to animals.

All newer antibiotics licensed in Canada in the last 25 years or so are only used, or prescribed for use, by veterinarians. These include drugs or drug classes used commonly in human medicine, including trimethoprim-sulfadoxine, sulbactam-ampicillin, ceftiofur, and cephapirin (the latter as an udder treatment for cows), as well as florfenicol, enrofloxacin (as an egg dip), and gentamicin (for newly hatched poultry, newborn pigs, or uterine infections in cows). These drugs may be used by farmers only under the direction of a veterinarian in the context of a valid client-veterinarian relationship. Veterinary prescription drugs are administered for short periods for prevention or treatment of diseases; they are not used in feed. Drugs in this category may be better used than feed antibiotics, since veterinarians are as well educated as physicians about the use of antibiotics. Perhaps 10% of total antibiotic use in agriculture falls into this category.

Drug use in agricultural animals is regulated under the Food and Drugs Act, as well as the Feeds Act, with licencing for agricultural use being through the Bureau of Veterinary Drugs, a small division of Health Canada. Feed, OTC, and veterinary prescription drugs have strict directions on the label describing quantity, the purpose for which it is used, and regulations relating to the time required to remove the drug from feed before animals are slaughtered. Only veterinarians may prescribe licensed drugs for "off label" use, which means use at a dosage, in a species, or for a purpose other than that for which the drug is licensed. Such use can only be in animals under the direct care of the veterinarian, and particular care has to be taken to respect the withdrawal period before animals are slaughtered, so that violative residues of the antibiotic are not present in the carcass.

There are comprehensive and extensive federal and provincial programs that monitor animal carcasses for illegal quantities of antibacterial drugs. Any trace amounts that are allowed are judged to be of no adverse significance. Although illegal residues were a problem at one time, particularly for sulfonamides in pig carcasses, the pass rate is now over 99.9% (3). Compliance with withdrawal periods to prevent illegal drug residues has become the central focus of agricultural use of antibiotics, because of the importance of providing safe, chemical free, and nutritious food. The financial penalties of noncompliance may, with the exception of milk, be inadequate. In the United States, penalties can be severe. For example, in January 1997, the president of Vitek Supply Corporation in Wisconsin was sentenced to 44 mo in prison and the company ordered to pay fines and restitution of over one million dollars for smuggling into and distributing within the United States unapproved antimicrobial drugs, including avoparcin and nitrofurans, and a toxic hormone-like drug called clenbuterol (4). Penalties in Canada would be considerably lighter.

The major points that emerge about the agricultural use of antibiotics are as follows: 1) Feed and OTC antibiotics are "older" drugs not often used in medicine and often unique to agriculture; 2) newer drugs are veterinary prescription only, and none are available for feed use; 3) use of antibiotics in farm animals is extensively regulated; and 4) effort and expense is made to ensure that none of these drugs reach people through their food.

The benefits of feed antibiotics in agriculture are considerable in terms of increased growth rates and increased feed efficiency, particularly in young animals. Estimates vary and, indeed, the beneficial effects of antibiotics in feed may be declining, but, in swine, their subtherapeutic use may improve the average daily weight gains of young pigs from 10% to 23% and feed efficiency by 6% to 8% (5). Among other advantages, this translates into land that can be released from farming for many purposes. Therapeutic and subtherapeutic antibiotic use results in significant reduction in illness, and in pain, suffering, and death caused by infections. In addition, carcass condemnations after slaughter because of disease are significantly reduced, an important feature in an industry with narrow profit margins.

While there are clearly benefits to the variety of antibiotic uses in agriculture, what are the risks?

The major risk is that antibiotic use can lead to drug resistance in pathogens of significance to humans, both directly, as has been shown in the case of foodborne pathogens such as *Campylobacter jejuni* and *Salmonella* spp., and possibly indirectly, by contributing antibiotic-resistant nonpathogens, which can colonize humans for variable periods. Although these resistant nonpathogens themselves may not cause disease in people, the *potentially* critical importance of this is that these nonpathogenic bacteria may transfer this resistance to bacteria capable of causing disease in people, because most antibiotic resistance can be transferred between bacteria through a variety of mobilizable genetic elements. This could have the effect of making these infections more difficult to treat. Direct resistance is to the particular antibiotic(s) used in animals. This, of course, would not usually be a problem for human medicine with the feed antibiotics unique to agriculture. Attention about this potential risk has focused particularly on subtherapeutic feed antibiotics as the potential major contributor to resistance transfer to human pathogens, because these are used in the greatest quantity. There is no doubt that agricultural uses of antibiotics select for antibiotic-resistant bacteria. It is axiomatic that antibiotic use selects for antibiotic resistance in a process of Darwinian selection, as all forms of medicine have found to their cost. The fittest, resistant, bacteria survive this selection. The critical and unanswered question is how much this selection contributes to resistance important in human medicine.

Whether feed antimicrobial use in animals contributes to sickness and death in people has been the subject of major, repeated, and inconclusive reviews by blue-ribbon government-sponsored committees (1,6–10). Nearly 30 y ago, following the Swann Report (6), the British government withdrew the use of antibiotics

useful in human medicine from unrestricted feed use by farmers. Twenty years ago, the U.S. Food and Drug Administration withdrew its similar proposal to stop subtherapeutic feed use of penicillin and tetracyclines in animals, because opponents were convinced that there was inadequate evidence for the adverse effects of such use (10). The theoretical basis for concern that antibiotic use in agriculture, particularly that associated with feed use, may foster infections by drug-resistant pathogens in humans is immense, but direct evidence of its reality has been sparse. One recent U.S. report focused on the risks of antibiotic resistant *Salmonella* spp. from animals causing deaths in people. In a statistical approach, which is not easy to follow, it was calculated that "the likeliest estimate of excess deaths attributable to subtherapeutic uses of penicillin and/or the tetracyclines ... is in the range of 6 per year" and that "the likeliest estimate of deaths ... arising because of 'increased difficulty of treating' is 20 per year" (1).

It is also interesting to note that the withdrawal of antibiotics useful in human medicine as feed antibiotics in the European Economic Community (EEC) has not had a noticeable effect on *Salmonella* spp. resistance, possibly because the same antibiotics are being prescribed by veterinarians for therapeutic use (11).

Studies of antibiotic-resistant *Escherichia coli*, a commensal of the human and animal intestine, have revealed that many are derived from food. People, such as transplant patients or astronauts fed food sterilized by irradiation, have shown dramatic drops in resistant *E. coli* in their feces, as well as marked drops in total numbers of this bacterium (12). Conversely, a study of vegetarians showed that they had slightly more resistant *E. coli* than did meat eaters (13), suggesting that vegetables are also among the sources of some resistant bacteria. As the 1995 Office of Technology Assessment (OTA) reported to the U.S. Congress, a comprehensive study of the sources of antibiotic-resistant bacteria in the human diet might lead to informed interventions to reduce bacterial contamination in food handling processes (10). Although we need to determine what the actual contribution of feed antibiotics is to antibiotic-resistance in human pathogens, designing effective and affordable studies to answer this question may be extremely difficult because of the complexities of the microbiology involved (10). My prediction would be that such a study, if it could be done, would find that overall, compared with the medical use of antibiotics, feed antibiotic use makes an insignificant contribution to the sum total of resistance in human pathogens. With hindsight, however, because of the resistance potential, probably no medically useful antibiotic should ever have been approved for feed use. It is unlikely that any new, medically useful, feed antibiotics will ever be licensed.

Two recent issues in the battlefield of agricultural use of antibiotics may point out some weaknesses in Canadian policy.

The 1st battle was the licensing recently in the United States of sarafloxacin, a new fluoroquinolone drug, for use in water to treat *E. coli* infections in meat poultry. After an intensive public hearing on this issue, the Center for Veterinary Medicine issued a licence for use under veterinary prescription only for this specific purpose, with no leeway for extralabel use (14). In addition, an active program of monitoring of antimicrobial drug resistance in selected enteric pathogens people can acquire from chickens (*Campylobacter jejuni*, *Salmonella* spp.) was instituted nationally. The concern about licensing this drug is that fluoroquinolones are the only important new class of antibiotics developed this decade and, unfortunately, antibiotic resistance develops readily in them. In Europe, where the drug class has been administered therapeutically to chickens in recent years, resistance to fluoroquinolones has developed in *Campylobacter jejuni* isolated from chickens, the major source of human infection (15). Would licensing of sarafloxacin or other fluoroquinolones in Canada be associated with public debate as robust as that in the United States? There is in Canada no discernable point for public input into the licensing process.

The 2nd recent major battle concerns avoparcin, a growth promoter used in chickens and pigs in Europe. The tragedy of avoparcin is that this drug was introduced as a growth promoter precisely because it had no use in human medicine and, therefore, had one of the ideal properties required of growth promoters (16). Unfortunately, avoparcin is a glycopeptide antibiotic similar to vancomycin, a drug used to treat infections caused in people by certain otherwise highly resistant gram-positive bacteria, notably enterococci. Enterococci are found normally in the intestines of people and animals and are virtually nonpathogens. When the extensive human intestinal microflora is eradicated by use of extremely broad-spectrum, bactericidal drugs as, for example, in patients being treated for certain tumors, this otherwise wimpy pathogen can multiply to high numbers, because it is inherently resistant to such drugs and has no bacterial competition to prevent its growth, and can invade the patient to cause septic or other illness. Enterococci also acquire resistance to vancomycin fairly readily. Vancomycin-resistant enterococci (VRE) have emerged recently as major pathogens of immunosuppressed, broad spectrum antibiotic-treated, human patients, an emergence compounded by the recent patent expiry on vancomycin. Inexpensive vancomycin generics have come into extensive hospital use.

It was realized recently in Denmark and in other parts of Europe that enterococci isolated from the intestines of chickens and pigs fed avoparcin were VRE (17–19). Within days, the Danish Minister of Health stopped all use of the drug in animals, a ban recently adopted in the rest of the EEC. Such a decisive step appears justified when combined with more judicious use of vancomycin and better infection control procedures in hospitals. The critical question for Canadian veterinary drug policy makers is whether and under what circumstances a similar ban might have been introduced in this country, should avoparcin have been used also here and in the United States? What mechanisms are in place to ensure both careful review and decisive action here? Denmark is a country with a public medical system and an impressive, long-term, and successful commitment to control of antibiotic resistance in human pathogens. What is Canada's national commitment and where is the mechanism for ensuring such commitment? With health a provincial issue, and a federal government focused

on reducing the deficit, will control of antibiotic resistance fall, like so much else, between cracks in the constitution?

Agricultural use of antibiotics may currently be unfairly blamed for resistance in human pathogens. At the recent Health Canada conference on antimicrobial resistance held in Montreal, the audience was told that perhaps only one-quarter of medical usage of antibiotics was appropriate. Although medicine clearly needs to improve its usage of antibiotics, there are problems in the agricultural use of antibiotics. These include a loophole allowing farmers to import drugs without regulation for use solely on their own farms, as well as evidence that OTC drugs are used ineffectively and inappropriately. There may be problems, associated with understaffing, within the Bureau of Veterinary Drugs, as suggested in the Globe and Mail (20). The small size of the Canadian market, combined with the slowness and expense of the animal drug licensing process, has made Canada a country of last resort in licensing of drugs by the transnational drug corporations, not only reducing Canadian international competitiveness but perhaps also encouraging drug smuggling and illegal use. We currently have no national program for monitoring antibiotic resistance in animal pathogens, such as *C. jejuni*, *E. coli* 0157:H7 ("the hamburger pathogen"), or *Salmonella* spp., which might usefully help to monitor illegal use of antibiotics, since there is a direct correlation between antibiotic use and resistance. Was the recent unusual "blip" in chloramphenicol resistance in some poultry *Salmonella* spp. (21) because one farm was illegally using the drug? It is encouraging, however, that, as a result of the Montreal conference, Health Canada is pursuing development of a national antibiotic-resistance surveillance scheme for farm animal-derived bacteria. Veterinarians (outside Quebec) are in a potential conflict of interest in prescribing veterinary use antibiotics, since they sell these for profit. Should we not introduce legislation like that of the U.S. Animal Drug Availability Act (1996) to prevent veterinarians selling the drugs they prescribe (22)?

As the 1995 OTA report (10) suggested, we need to restudy the benefits of feed antibiotics, especially the subtherapeutic use of these drugs. Is this practice still cost effective? How many farmers use these drugs without thinking, perhaps because of advertising or because antibiotic-free feed is not readily available? It would be a good idea for feed antibiotics to go through a streamlined relicensing process every 10 y. Agriculture needs to look at its use of antibiotics, promoting judicious use and focusing on reducing resistant bacteria getting into the human food chain, or into rivers through animal manure spread on fields, rather than focusing on residues in meat, which is no longer an issue. Reduction of microbial contamination of meat and poultry is now a focus of the meat industry. The Canadian Food Inspection Agency, working with industry, needs to continue its important efforts to prevent fecal contamination of meats during the slaughter process, since this will have the beneficial effect of reducing transfer of antibiotic-resistant bacteria.

The approach to the reduction of antimicrobial resistance must therefore be a rational process, based on national understanding and discussion of scientifically derived data about use and misuse; on the more judicious use of antibiotics in all sectors in Canada (and throughout the world) using these drugs, on resistance monitoring and interpretation; and on effective and informed medical, veterinary, and public input into the process. Alternative approaches to control of bacterial infections should be explored as ways of ensuring that what remains one of the miraculous developments of medicine is maintained for future generations. No one group should be unfairly scapegoated as a knee-jerk reaction to a multifactorial and complex issue.

References

1. Institute of Medicine. Human health risks with the subtherapeutic use of penicillins or tetracyclines in animal feed. Washington, DC: National Acad Pr, 1989.
2. Health Canada, Antimicrobial Resistance Conference, Montreal 1997 (data supplied by IMS Canada from private pharmacy prescriptions).
3. Agriculture and Agri-Food Canada. Annual report on chemical and biological testing of agri-food commodities, 1992/93. Ottawa: Agri-Food Safety and Strategies Division, Agriculture and Agri-Food Canada.
4. Anonymous. Vitek sentenced in smuggling case. FDA Vet 1997; 12(2): 11.
5. Hays VW. The Hays Report; Effectiveness of feed additive usage of antibacterial agents in swine and poultry production. Long Beach, California: Rachelle Lab.
6. Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (Swann Report). London: Her Majesty's Stationary Office, 1969.
7. Report to the Commissioner of the Food and Drug Administration by the FDA Task Force. The use of antibiotics in animal feeds. Rockville, Maryland: U.S. Government Printing Office, 1972.
8. U.S. Congress, Office of Technology Assessment. Drugs in livestock feed. Washington, DC: U.S. Government Printing Office, 1979.
9. National Research Council. The effects on human health of subtherapeutic use of antimicrobials in animal feeds. Washington, DC: National Acad Pr, 1980.
10. U.S. Congress, Office of Technology Assessment. Impacts of antibiotic-resistant bacteria. Washington, DC: U.S. Government Printing Office, 1995.
11. Linton AH. Has Swann failed? Vet Rec 1981; 108: 328–331.
12. Corpet DE. Antibiotic resistance from food. New Engl J Med 1988; 318: 1206–1207.
13. Elder HA, Roy I, Lehman S, Phillips RL, Kass EH. Human studies to measure the effect of antibiotic residues. Vet Hum Toxicol 1993; 35 (Suppl. 1): 31–36.
14. Anonymous. Update on fluoroquinolones. FDA Vet 1995; 10(6): 1–2.
15. Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP. Quinolone resistance in *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. J Antimicrob Chemother 1991; 27: 199–208.
16. Prescott JF, Baggot JD. Growth promotion and feed antibiotics. In: Prescott JF, Baggot JD, eds. Antimicrobial Therapy in Veterinary Medicine. 2nd ed. Ames: Iowa State Univ Pr, 1993: 562–568.
17. Aarestrup FM. Occurrence of glycopeptide resistance among *Enterococcus faecium* isolates from conventional and ecological poultry farms. Microb Drug Resist 1995; 1: 255–257.
18. Bates J, Jordens ZJ, Griffiths DT. Farm animals as a putative reservoir for vancomycin-resistant enterococcal infection in man. J Antimicrob Chemother 1994; 34: 507–516.
19. Klare I, Heier H, Claus H, Reissbrodt R, Witte W. *vanA*-mediated high-level glycopeptide resistance in *Enterococcus faecium* from animal husbandry. FEMS Microbiol Lett 1995; 125: 165–172.
20. Eggertson D. Drug-approval process criticized. Globe and Mail 1997, May 28, Sect A:1, A:10.
21. Poppe C, McFadden KA, Demczuk WHB. Drug resistance, plasmids, biotypes and susceptibility to bacteriophages of *Salmonella* isolated from poultry in Canada. Int J Food Microbiol 1996; 30: 325–344.
22. Anonymous. Veterinary feed directive drugs. FDA Vet 1997; 12(2): 1–2.